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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/629,261	07/28/2003	Zheng Xin Dong	00537-186003	6695

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EXAMINER	
LUKTON, DAVID	
ART UNIT	PAPER NUMBER
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/629,261	DONG, ZHENG XIN	
	Examiner	Art Unit	
	David Lukton	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-11 and 19* is/are allowed.

6)☒ Claim(s) *12-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Pursuant to the directives of the response filed 2/5/07, claims 1, 4, 11, 15 have been amended. Claims 1-16 & 19 remain pending. The non-elected claims are now rejoined with the elected claims. Claims 1-16 and 19 are examined in this Office action.

Applicants' arguments filed 2/5/07 have been considered and found persuasive. The rejections that were imposed in the prior Office action are now withdrawn.

Claims 1-11 & 19 are now characterized as allowable.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have provided evidence (declaration filed 2/5/07) showing that several compounds of the claimed invention exhibit binding to cells which contain GLP-1 receptors. The issue now is whether or not claims 12-14 are enabled.

Applicants are proposing that the compounds of claim 1 will be effective to treat all of the diseases recited in claim 13. However, there is no evidence that even one of the recited diseases can be effectively treated. One issue is that applicants have not determined whether the peptides of claim 1 are agonists or antagonists of the GLP-1 receptor. Applicants do not know whether the claimed peptides stimulate insulin secretion from *beta*-cells, or whether the peptides inhibit the same. Applicants do not even know if adenylyl cyclase activity is affected one way or another by the peptide.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. Consider the following:

- Torsello, Antonio (*Endocrinology* **143** (5) 1968, 2002) pertains to growth hormone, and discloses that stimulation of the growth hormone secretagogue receptor does not correlate with capability to stimulate GH secretion.

- McFadyen "Modifications of the cyclic mu receptor selective tetrapeptide Tyr-c[D-Cys-Phe-D-Pen]NH_2 (Et): effects on opioid receptor binding and activation" (*Journal of Peptide Research* (2000 Mar) **55** (3) 255-61) reported on modifications to the title peptide. The reference discloses that potency changes did not always correlate with affinity, suggesting that the conformation required for binding and the conformation required for activation of the opioid receptors are different.

- Keith , "mu-Opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain" (*Molecular Pharmacology* **53** (3) 377-84, 1998) discloses that the different effects of individual agonists are not correlated with their potencies for receptor activation and that a variety of clinically important agonists differ significantly in their relative abilities to stimulate the rapid internalization of opioid receptors.

- Xiao (*Biochemistry* **40**, 2860, 2001) has looked at the relationship between cAMP production in cells, and *in vivo* activity. While some degree of correlation was noted, a 1:1 correspondence was absent. As stated on page 2864, col 2, "the results indicated that these functions may be dissociated, mostly likely to additional determinantants of *in vivo* activity...". For example, as conveyed in table 6, Phe'-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 along with decreased *in vivo* insulinotropic activity; by contrast, Acetyl-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 accompanied by an increase in *in vivo* insulinotropic activity. Thus, receptor activation is not necessarily predictive of *in vivo* activity.

- Lunec, "MSH receptor expression and the relationship to melanogenesis and metastatic activity in B16 melanoma" (*Melanoma Research* (1992 May) **2** (1) 5-12) compared the effects of different pro-opiomelanocortin (POMC) peptides on melanogenesis and metastasis and their relationship to MSH receptor expression in B16F1 melanoma cells. The authors disclose that the relative binding affinities of the different peptides, measured by displacement of [125I]-Nle4-D-Phe7-alpha-MSH, did not closely correlate with the relative potencies in stimulating melanogenesis and metastasis. This suggests that receptor activation and the subsequent biological response is not determined solely by binding affinity.

- Miyagi, M. (*Biol Pharm Bull* 19, 1210-13, 1996) discloses that bromocriptine binds to the D1 and D2 receptor, but is inactive *in vivo*.

In accordance with the foregoing, it is clear that whether one is endeavoring to stimulate a receptor *in vitro* or to antagonize a receptor *in vitro*, extrapolating to a therapeutic method leads to "unpredictable" results.

Consider next the matter of endeavoring to treat an ill patient afflicted with diabetes. Each of the following references teaches "failure" in the treatment of diabetes:

- Nasushita R., "A case of acromegaly accompanied by adrenal preclinical Cushing's syndrome" (*Endocrine Journal* **46** (1) 133-7, 1999);

- O'Keefe J H Jr, "Improving the adverse cardiovascular prognosis of type 2 diabetes" (*Mayo Clinic Oroceedings* **74** (2) 171-80, 1999).

- Warner D P "Mortality and diabetes from a population based register in Yorkshire 1978-93" *Archives of Disease in Childhood* 78 (5) 435-8, 1998)

- Maruyama Y, "A case of insulin dependent diabetes mellitus following systemic treatment for Vogt-Koyanagi-Harada syndrome" (*Ophthalmic Surgery and Lasers*, **31** (6) 487-90, 2000)

- Wandell P E "Drug prescription in diabetic patients in Stockholm in 1992 and 1995 - - change over time" (*European Journal of Clinical Pharmacology* **52** (4) 249-54, 1997)

- Mak K. H., "Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries" (*Journal of the American College of Cardiology* **30** (1) 171-9., 1997)

- Zuanetti G., "Influence of diabetes on mortality in acute myocardial infarction: data from the GISSI-2 study" (*Journal of the American College of Cardiology* **22** (7) 1788-94, 1993).

The reality in pharmacology is that receptor binding does not equate with receptor activation. More often it is receptor antagonism that results. If applicants choose to respond by arguing that receptor binding invariably leads to

receptor activation, applicants will be requested to explain how it is that they would go about demonstrating receptor antagonism. The fact is that GLP-1 antagonists are known; the claimed peptides may well be antagonists, merely competing with GLP-1 for access to the receptor.

Perhaps applicants will be able to provide evidence to support the proposition that one or more of the claimed compounds will be effective to treat diabetes. But should this event come to pass, a number of other questions will remain. For example, even if the compounds are effective to treat diabetes, why would the skilled artisan believe that any and all "metabolic disorders" can be successfully treated? Most troubling is the proposition that any and all "neurodegenerative diseases" can be successfully treated. These diseases would include the following:

> AIDS Dementia Complex (a.k.a. HIV-Associated Dementia) Amyotrophic Lateral Sclerosis (a.k.a. Lou Gehrig's Disease), Alzheimer 's Disease, Huntington's Disease, Multiple Sclerosis, Parkinson's Disease, Creutzfeldt-Jakob disease, progressive supranuclear palsy, Creutzfeldt-Jakob disease, multifocal leukoencephalopathy, diffuse and transitional Lewy body disease, frontotemporal degeneration, corticobasal degeneration, multiple system atrophy, Pick Disease, argyrophilic grain disease and corticobasal degeneration

There is no reason to believe that any of these can be successfully treated by a GLP-1 receptor agonist, and no reason to believe that any of these can be successfully treated by a GLP-1 receptor antagonist. As matters currently stand, "undue experimentation" would be required to practice the claimed invention.

✧

Claims 12, 13, 15, 16 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 12 is indefinite as to the intended agonist effects.

- Claim 13 is indefinite as to the intended metabolic disorders and indefinite as to the intended "central nervous system diseases".

- Claim 15 recites two peptides that contain a glycine at position 8, and one that recites a serine at position 8. The peptides in question are those of SEQ ID NOS: 31, 32 and 34. Claim 1, however, precludes the possibility that a peptide can have a glycine at position 8, or a serine at position 8. Accordingly, claim 15 is not properly subgeneric to claim 1. One option would be to cast claim 15 in independent form. Another option would be to delete the three peptides in question from claim 15, and to create a new claim (which is independent) that recites the three peptides. Note that the same issue applies in the case of claim 16 as well.

✧

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (571)272-0562. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON, PH.D.
PRIMARY EXAMINER